(11) (A) No. 1103314

(45) ISSUED 810616

(52) CLASS 326-12

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(51) INT. CL. A61B 5/00, A61M 5/00

(19) (CA) **CANADIAN PATENT** (12)

(54) ARTIFICIAL BETA CELL FOR CONTROLLING A QUANTITY OF INSULIN INFUSION

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(21) APPLICATION No. 297,510

(22) FILED 780221

No. OF CLAIMS 3

This invention relates to an improved artificial beta cell for controlling a quantity of insulin infusion, especially to normalize blood glucose concentrations of diabetics on a minute-by-minute basis.

The discovery of insulin in 1921 allowed the successful treatment of the acute manifestations of diabetes. But the replacement therapy by intermediate-acting insulin injection once a day for diabetics was revealed to be ineffective to normalize the blood glucose concentration, especially in the post-prandial period. Thus, high glucose levels of diabetics seem to result in the onset or progress of the chronic complications.

Recently with introduction of the computer, new techniques for elaborating the measurement, communication and operation to achieve the adaptive control have been developed in some fields of medicine.

The artificial endocrine pancreas which infuses insulin and glucose in relation to the blood concentrations measured by rapid chemical determinations on continuous blood sampling has been developed and reported from a few institutes (Albisser et al. 1974a,b; Pfeiffer et al. 1974; Kerner et al. 1976). In these systems, when blood glucose levels were going down to the levels of around 120 mg/100 ml, the rate of insulin infusion was 600 mU/min in 81kg man (Albisser et al. 1974b). By our calculation, this is equivalent to 33 x B (hereinafter defined), so peripheral plasma insulin concentration would be 300 μU/ml, higher than the upper limits of physiological ranges. In another paper (Kerner et al. 1976), following the 100 g glucose oral administration, the rate of insulin infusion was between 400 and 600 mU/min. In both cases, those high rates of insulin infusion resulted in hypoglycemia which made it necessary to infuse glucose.

To make up computer algorithm of our artificial beta cell, we tried to simulate the insulin response in the blood glucose regulatory system. With the aid of proportional and derivative mode of control, we could simulate the glucose-induced insulin secretion.

Two important characteristics reside in our artificial beta cell, the first is that because insulin is infused in a proportional plus derivative action to blood glucose concentration, so the rate of insulin infusion is small enough to keep the plasma concentration of insulin physiological; thus insulin requirements are reduced to around a half of those given subcutaneously. The second is that glucose or glucagon infusion to restore hypoglycemia is not necessarily needed.

As a result of study in the effect of insulin on the rate of change in glucose concentration (i.e. derivative action) in glucose tolerance, it has been found that when the derivative action was added to the proportional action properly in insulin infusion regulatory system, the insulin requirement was the smallest and glucose regulation was the best among experimental groups. It has been also found that when insulin infusion was based only on the blood glucose concentration, it could not regulate the glucose assimilation curves following intravenous glucose challenge and what is worse, late hypoglycemia occurred. In this specification, the term "proportional action" means that insulin secretion responds to the glucose concentration per se, whereas the term "derivative action" means that the insulin secretion responds to the rate of change in glucose concentration.

Therefore, a principal object of the invention is to provide an artificial beta cell for controlling a quantity of insulin infusion comprising a glucose-senor for continuously measuring blood glucose concentration, a computing circuit for calculating a quantity of glucose, forecasted blood rate every

minutes, in which a real quantity of insulin required is calculated in the computing circuit based on the blood glucose concentration and the rate of change in blood glucose concentration depending on an individual basis.

In the apparatus according to the invention, the real quantity of insulin required is computed in the computing circuit in accordance with the following equation:

$$I.I.A. = \theta\{KED \times a \times \overline{BS} + (a + b \times KED)\,\Delta\overline{BS} + c \times KED\} \quad .....(1)$$

wherein I.I.A. is insulin infusion rate (μU/min.), θ is insulin space (body weight x $\frac{16.7}{100}$ (ml)), ED is insulin degradation rate (min^{-1}), K is diffusion constant (dimensionless), $\overline{BS}$ is blood glucose concentration (mg/100ml), $\Delta\overline{BS}$ is rate of change in blood glucose concentration (mg/100ml.min.) and a, b and c are intrinsic constants for an individual (for example patient), i.e.

a : 100μU/mg

b : 100μU.min/mg

c : μU/ml

The equation (1) could be obtained by the following assumptions. Namely, plasma insulin concentration $\overline{IRI}$ may be represented with two independent variables, i.e. the one is the blood glucose concentration $\overline{BS}$ (mg/100ml), the other is the rate of change in blood glucose concentration $\Delta\overline{BS}$ (mg/100ml.min.), as follows:

$$\overline{IRI} = a \times \overline{BS} + b \times \Delta\overline{BS} + c \quad .....(2)$$

wherein a, b and c are intrinsic constants for an individual. Next, the exogenously administered insulin is distributed into the insulin space and degraded by the liver and other organs, then diffused uniformly to reflect the insulin concentration in peripheral vein. This phenomenon was expressed in the following:

$$\frac{d\,(\theta \cdot \overline{IRI})}{dt} = I.I.A. - K \cdot \theta \cdot \overline{I\ R\ I} \cdot D \quad .....(3)$$

wherein $\overline{IRI}$ is plasma insulin concentration in peripheral vein

(μU/ml), I.I.A. is insulin infusion rate (μU/min), θ is the insulin space (g), ED is insulin degradation rate (min^{-1}), and K is diffusion constant (dimensionless). As the $\overline{IRI}$ is difficult to be analyzed within a short time, this factor $\overline{IRI}$ is eliminated from the equations (2) and (3), resulting in the above-described equation (1).

In the equation (1) according to the invention, the maximum quantity of insulin infusion is preferably established at the quanitity 30 times as much as that of the basal insulin infusion necessary for normal metabolism of glucose.

Other objects and advantages of the invention will become obvious after considering the discussion of the invention in connection with the preferred embodiments thereof shown in the accompanying drawings in which:

Figure 1 is a systematic view of the artificial beta cell according to the present invention;

Figures 2, 3, 4 and 5 are graphic curves showing the glucose assimilation curve and insulin infusion pattern.

Figure 1 shows a fundamental structure of the apparatus according to the invention, in which the blood glucose concentration is determined by a glucose-sensor 12 for a diabetic 10 which has malfunction in secretion of insulin. A signal of blood glucose concentration thus determined by the glucose sensor 12 is transmitted to a printer 14, which actuates a computing circuit 16 having a predetermined program for calculating a proper quantity of insulin infusion to the diabetic and controls a pump 18 for injecting the corresponding quantity of insulin from a storing vessel 20 of insulin to the diabetic 10.

In the apparatus according to the invention, the computing circuit 16 calculates the proper quantity of insulin infusion in accordance with the following equation:

$$I.I.A. = \theta\{KED \times a \times \overline{BS} + (a + b \times KED)\ \Delta\overline{BS} + c \times KED\}$$

in which I.I.A. is insulin infusion rate (μU/min.), θ is insulin space (body weight x $\frac{16.7}{100}$ (ml)), ∋D is insulin degradation rate (min^{-1}), K is diffusion constant (dimensionless), $\overline{BS}$ is blood glucose concentration (mg/100 ml), $\Delta\overline{BS}$ is rate of change in blood glucose concentration (mg/100ml.min.), and a, b and c are intrinsic constants for an individual, i.e. a : 100μU/mg

b : 100μU.min/mg

c : μU/ml

In order to determine the suitable values for a, b and c in the equation (1), glucose solution was administered as intravenous glucose pulse loads to normal dogs, and data were obtained when $\Delta\overline{BS}$ was below zero and when $\Delta\overline{BS}$ was above zero during which time 20mg/Kg.min. of glucose was administered persistently for 60 minutes. The data thus obtained were analyzed with the aid of multiple regression analysis to obtain the following values :

$\Delta BS>0$: a = 0.137, b = 4.10, c = 1.95

$\Delta BS<0$: a = 0.088, b = -1.29, c = 2.20

The insulin space θ is determined by the method of Sherwin et al and found to be 0.167 x body weight (g).

The insulin degradation rate ∋D is determined by the method of Stimler and found to be 0.148 min^{-1}.

The diffusion constant K (dimensionless) is determined by utilizing a depancreatized dog and analyzing the relationship between a quantity of insulin infusion and an insulin level in peripheral vein, and found to be 1.46. However, it has been confirmed that the clinically suitable value of K is 1.2.

In the following, the examples according to the present invention are illustrated.

Example 1 (Intravenous glucose pulse loads test)

Glucose was injected into a juglar vein of a depancreatized dog in an amount of 0.33 g glucose per Kg of body weight

in 10 seconds, and thereafter blood glucose concentration is determined over a period of 80 minutes. After discontinuation of insulin infusion to the dog for more than 24 hours and with fasting for 16 hours, 5000 μU/Kg.min. of insulin was persistently injected into peripheral vein. When the blood glucose level was reduced to 120mg/100ml, the quantity of insulin injection was reduced to 225 μU/Kg.min. (herein, this quantity is referred to as B, representing the basal insulin infusion). Then, it has been observed that when finishing the insulin injection after the intravenous glucose pulse loads the blood glucose concentration was reduced to 170 mg/100ml over a period of 40 to 60 minutes but thereafter started to increase again.

Under the similar condition, insulin was injected to the depancreatized dog in an amount of 100 x B for the first one minute, which amount corresponds to the insulin level in portal blood which had been obtained by applying the glucose loads test to normal dogs, and thereafter injected persistently in an amount of 10 x B. In this case, it has been observed that the glucose assimilation curve is slightly delayed in contrast to that of a noraml dog and that the utilization constant of glucose (K value) was normal (3.1 ± 0.3). However, when the insulin injection was maintained in the amount of 10 x B, hypoglycemia was observed after 80 minutes (Figs. 2a and 2b).

Based on the above observation, insulin was injected according to the predetermined program in such a manner that the maximum insulin infusion was set to the quantity of 30 x B. The results are shown in Figs. 3a and 3b. The Figures show that the blood glucose concentration per se and the rate of change in blood glucose concentration became higher for the first one minute due to the rapid and large dose of glucose. According to the calculation from the equation (1), a quantity of 177 x B of insulin was needed, but actually 30 x B of insulin was

injected based on the programming. As a result, only 3 x B of insulin was sufficient thereafter to regulate the blood glucose level in the similar pattern as in Fig. 2a (see Fig. 3a). Further, 80 minutes later the quantity of insulin required was reduced to B, but the blood glucose level could be maintained in the normal range without causing hypoglycemia. Thus, by employing the programming dosage, total insulin consumption could be reduced to 50% or less of that required in Fig. 2b (see Fig. 3).

Example 2 (Oral glucose loads test)

While insulin was orally administered to the depancreatized dog in an amount of B to maintain the normal blood glucose level, 2.0g per Kg body weight of glucose was administered. While continuously administering insulin in an amount of B, the change in blood glucose concentration was determined for 3 hours. The results are shown in Figs. 4a and 4b. On the other hand, insulin was administered according to the predetermined program as described in Example 1, about 3 x B of insulin could regulate the blood glucose in the normal range over the period of 4 hours (see Figs. 5a and 5b).

Example 3 (Medical test for diabetic coma)

Hitherto, it has been a principle to administer a large dosage of insulin for the medical treatment of diabetic coma and diabetic ketoacidosis.

Discontinuation of insulin treatment for 3 to 9 days caused serious diabetic ketoacidosis in the depancreatized dog. Then, an insulin solution in an amount of 5 x B to 100 x B was injected to the dog persistently for at least 3 hours. The insulin solution had been prepared by adding insulin Actrapid (a trade mark) to a physiological saline solution containing 0.5% of gelatine. Determination of the rate of drop in blood glucose revealed that the maximum average rate of drop (121mg/dl/hr.) was achieved

by using the quantity of 30 x B of insulin, and that better results had never been obtained with larger quantity than 30 x B.

According to the present invention, the quantity of insulin necessary to maintain the blood glucose level in the normal range can be reduced greatly, as well as can be calculated on the individual basis due to the factors, a, b, c and θ in the above-described equation (1).

THE EMBODIMENTS OF THE INVENTION IN WHICH AN EXCLUSIVE PROPERTY OR PRIVILEGE IS CLAIMED ARE DEFINED AS FOLLOWS:

1. An artificial beta cell for controlling a quantity of insulin infusion comprising a glucose-sensor for continuously measuring blood glucose concentration, a computing circuit for calculating a quantity of insulin infusion corresponding to the measured blood glucose concentration, an infusing means of insulin and a printer for registering the time, the measured blood glucose, forecasted blood glucose and insulin infusion rate every minute, in which a real quantity of insulin required is calculated in the computing circuit based on the blood glucose concentration and the rate of change in blood glucose concentration depending on individual basis in accordance with the following :

$$I.I.A. = \theta [K \cdot {}^{H}D \times a \times \overline{BS} + (a b \times K \cdot {}^{H}D) \Delta\overline{BS} + c \times K \cdot {}^{H}D]$$

wherein I.I.A. is insulin infusion rate (μU/min.), θ is insulin space (ml), ${}^{H}D$ is insulin degradation rate (min.$^{-1}$), K is diffusion constant (dimensionless), $\overline{BS}$ is blood glucose concentration (mg/100ml), $\Delta\overline{BS}$ is rate of change in blood glucose concentration (mg/100ml.min.) and a, b and c are intrinsic constants for an individual, i.e.

a : 100μU/mg (as unit)

b : 100μU.min/mg (as unit)

c : μU/ml

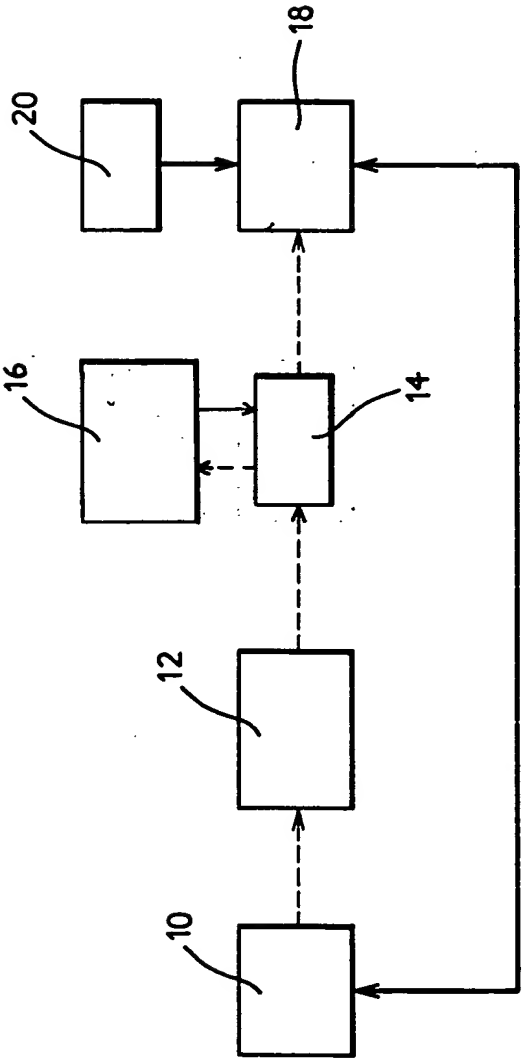

FIG.1

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2. The artificial beta cell according to claim 1 in which the quantity of insulin infusion does not exceed 30 times as much as that of the basal insulin infusion necessary for normal metabolism of glucose.

3. An artificial beta cell for controlling the infusion of insulin to a patient comprising a glucose-sensor for continuously measuring blood glucose, a computing circuit for calculating the rate of insulin infusion responsive to the measured blood glucose concentration and the rate of change of such concentration, a source of insulin and means responsive to said calculation for infusing said patient with a real quantity of insulin at the calculated rate, said computer circuit comprising a first element for determining the blood sugar concentration $\overline{BS}$ (mg/100ml); a second element for determinig the rate of change of said blood sugar concentration, $\Delta\overline{BS}$ (mg/100ml.min); and means for receiving and storing the values of:

insulin degradation, $\mathfrak{H}D$ (min^{-1});

insulin space in patient, θ (ml)

insulin diffusion constant , K

intrinsic constants for patient,

a : 100μU/mg (as unit)

b : 100μU.min/mg (as unit)

c : μU/ml

and means for calculating the rate of infusion I.I.A. (μU/min), in accordance with the following relationship;

$$I.I.A. = \theta[\, K\,\mathfrak{H}D \times a \times \overline{BS} + (\, a + b \times K\,\mathfrak{H}D\,)\,\Delta\overline{BS} + c \times K\,\mathfrak{H}D\,] .$$

FIG.3a

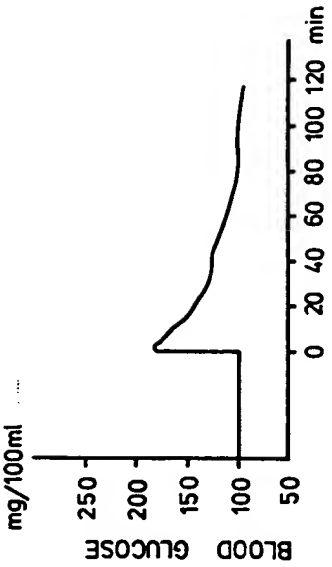

FIG.3b

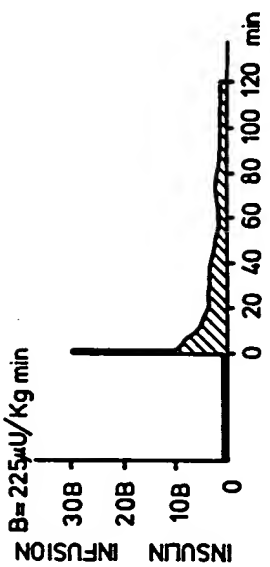

FIG.2a

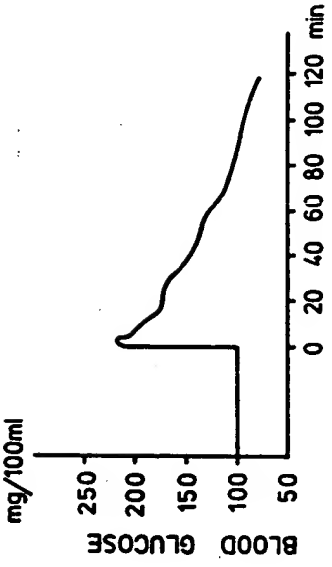

FIG.2b

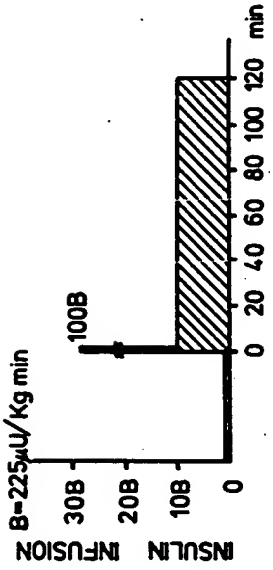

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FIG.4a

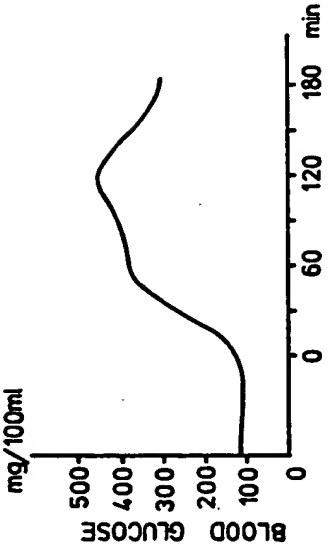


FIG.4b

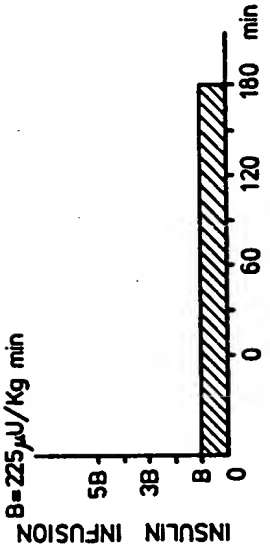


FIG.5a

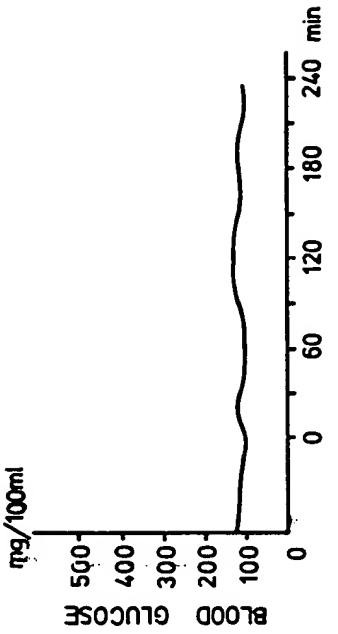
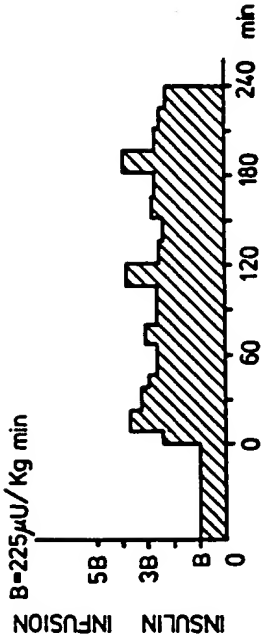


FIG.5b



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